CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074949**

Trade Name : CLOZAPINE TABLETS 25MG AND 100MG

Generic Name: Clozapine Tablets 25mg and 100mg

Sponsor : Zenith Goldline Pharmaceuticals, Inc.

Approval Date: November 26 , 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074949

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Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074949

APPROVAL LETTERS

ANDA 74-949

NOV 26 1997

Zenith Goldline Pharmaceuticals, Inc.
Attention: Jason A. Gross, Pharm. D.
140 Legrand Ave.
Northvale, NJ 07647

Dear Sir:

This is in reference to your abbreviated new drug application dated August 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Clozapine Tablets, 25 mg and 100 mg.

Reference is also made to your amendments dated May 28, June 2, June 20, July 30, September 12, October 17, November 5, and November 21, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Clozapine Tablets, 25 mg and 100 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Clozaril Tablets, 25 mg and 100 mg, respectively, of Novartis Pharmaceuticals Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

for

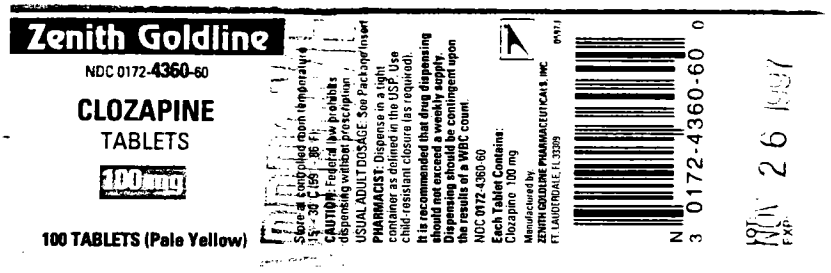
Douglas L. Osborn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11-26-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074949

FINAL PRINTED LABELING


Zenith Goldline
NDC 0172-4360-60
CLOZAPINE
TABLETS
100 mg
100 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-60
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
N 3 0172-4360-60 0
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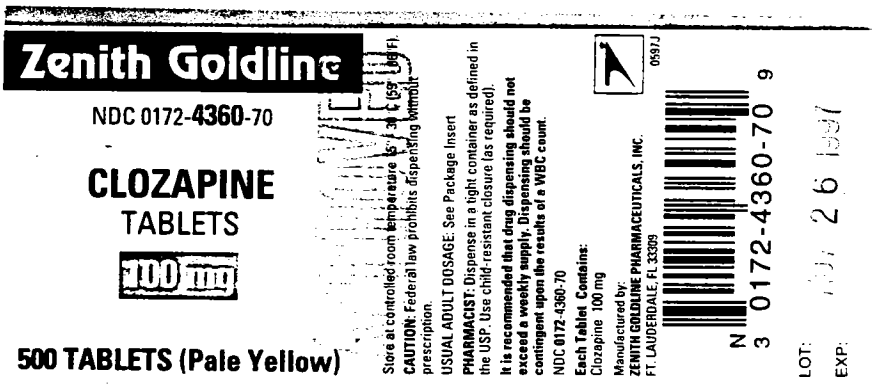
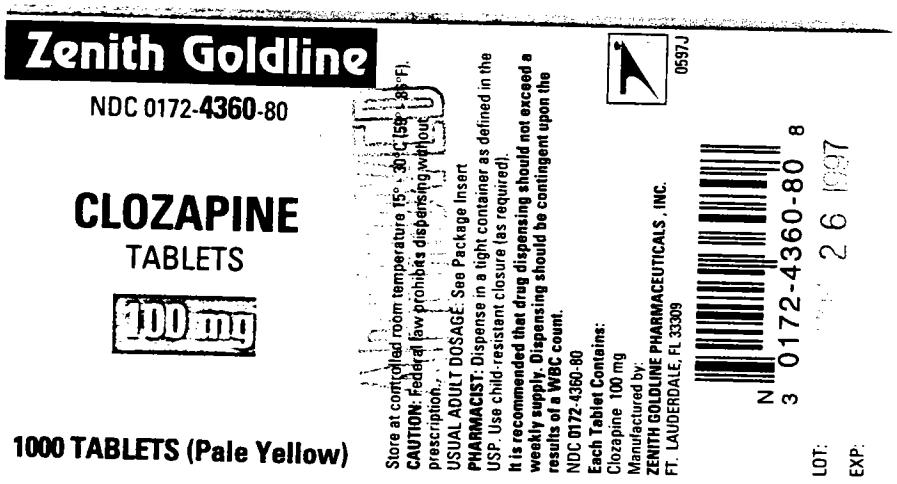
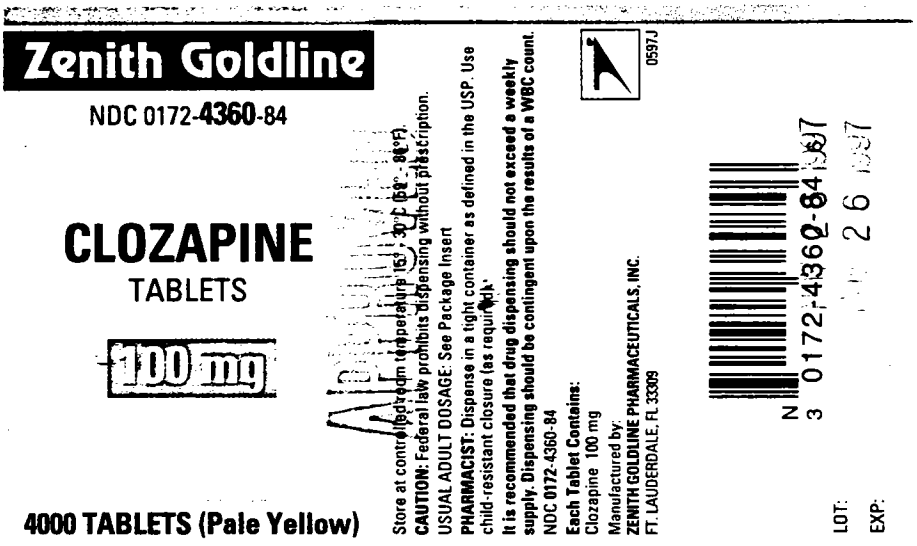
EXP:


Zenith Goldline
NDC 0172-4360-70
CLOZAPINE
TABLETS
100 mg
500 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-70
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
N 3 0172-4360-70 9
LOT:
EXP:


Zenith Goldline
NDC 0172-4360-80
CLOZAPINE
TABLETS
100 mg
1000 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-80
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
N 3 0172-4360-80 8
LOT:
EXP:


Zenith Goldline
NDC 0172-4360-84
CLOZAPINE
TABLETS
100 mg
4000 TABLETS (Pale Yellow)
Store at controlled room temperature 15° - 30°C (59° - 86°F).
CAUTION: Federal law prohibits dispensing without prescription.
USUAL ADULT DOSAGE: See Package Insert
PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).
It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.
NDC 0172-4360-84
Each Tablet Contains:
Clozapine 100 mg
Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309
0597J
N 3 0172-4360-84
LOT:
EXP:

142c

Zenith Goldline

NDC 0172-4359-85

CLOZAPINE

TABLETS

25 mg

5000 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.

NDC **0172-4359-85**

Each Tablet Contains:
Clozapine 25 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4359-85 7

LOT:

EXP:

Zenith Goldline

NDC 0172-4359-80

CLOZAPINE

TABLETS

25 mg

1000 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.

NDC **0172-4359-80**

Each Tablet Contains:
Clozapine 25 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS , INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4359-80 2

LOT:

EXP:

Zenith Goldline

NDC 0172-4359-70

CLOZAPINE

TABLETS

25 mg

500 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.

NDC **0172-4359-70**

Each Tablet Contains:
Clozapine 25 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4359-70 3

LOT:

EXP:

Zenith Goldline

NDC 0172-4359-60

CLOZAPINE

TABLETS

25 mg

100 TABLETS (Pale Yellow)

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

USUAL ADULT DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

It is recommended that drug dispensing should not exceed a weekly supply. Dispensing should be contingent upon the results of a WBC count.

NDC 0172-4359-60

Each Tablet Contains:
Clozapine 25 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC
FT. LAUDERDALE, FL 33309

0597J

N 3 0172-4359-60 4

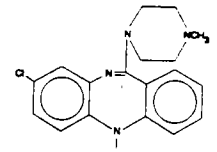
LOT:

EXP:

CLOZAPINE TABLETS

DESCRIPTION

Clozapine, an atypical antipsychotic drug, is a tricyclic dibenzodiazepine derivative. The chemical name of clozapine is 8-chloro-11-(4-methyl-1-piperazinyl)-5*H*-dibenzo [*b,e*][1,4] diazepine and it has the following structural formula:



$C_{18}H_{19}ClN_4$ M.W.326.83

Clozapine is a yellow, crystalline powder, very slightly soluble in water. Each tablet, for oral administration, contains 25 mg or 100 mg clozapine. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch and talc.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clozapine is classified as an "atypical" antipsychotic drug because its profile of binding to dopamine receptors and its effects on various dopamine mediated behaviors differ from those exhibited by more typical antipsychotic drug products. In particular, although clozapine does interfere with the binding of dopamine at D_1, D_2, D_3 and D_5 receptors, and has a high affinity for the D_4 receptor, it does not induce catalepsy nor inhibit apomorphine-induced stereotypy. This evidence, consistent with the view that clozapine is preferentially more active at limbic than at striatal dopamine receptors, may explain the relative freedom of clozapine from extrapyramidal side effects.

Clozapine also acts as an antagonist at adrenergic, cholinergic, histaminergic and serotonergic receptors.

Absorption, Distribution, Metabolism and Excretion

In man, clozapine tablets (25 mg and 100 mg) are equally bioavailable relative to a clozapine solution. Following a dosage of 100 mg b.i.d., the average steady state peak plasma concentration was 319 ng/mL (range: 102-771 ng/mL), occurring at the average of 2.5 hours (range: 1-6 hours) after dosing. The average minimum concentration at steady state was 122 ng/mL (range: 41-343 ng/mL), after 100 mg b.i.d. dosing. Food does not appear to affect the systemic bioavailability of clozapine. Thus, clozapine may be administered with or without food.

Clozapine is approximately 97% bound to serum proteins. The interaction between clozapine and other highly protein-bound drugs has not been fully evaluated but may be important. (See **PRECAUTIONS**)

Clozapine is almost completely metabolized prior to excretion and only trace amounts of unchanged drug are detected in the urine and feces. Approximately 50% of the administered dose is excreted in the urine and 30% in the feces. The demethylated, hydroxylated and N-oxide derivatives are components in both urine and feces. Pharmacological testing has shown the desmethyl metabolite to have only limited activity, while the hydroxylated and N-oxide derivatives were inactive.

The mean elimination half-life of clozapine after a single 75 mg dose was 8 hours (range: 4-12 hours), compared to a mean elimination half-life, after achieving steady state with 100 mg b.i.d. dosing, of 12 hours (range: 4-66 hours). A comparison of single-dose and multiple-dose administration of clozapine showed that the elimination half-life increased significantly after multiple dosing relative to that after single-dose administration, suggesting the possibility of concentration dependent pharmacokinetics. However, at steady state, linearity dose-proportional changes with respect to AUC (area under the curve), peak and minimum clozapine plasma concentrations were observed after administration of 37.5 mg, 75 mg, and 150 mg b.i.d.

Human Pharmacology

In contrast to more typical antipsychotic drugs, clozapine therapy produces little or no prolactin elevation.

As is true of more typical antipsychotic drugs, clinical EEG studies have shown that clozapine increases delta and theta activity and slows dominant alpha frequencies. Enhanced synchronization occurs, and sharp wave activity and spike and wave complexes may also develop. Patients, on rare occasions, may report an intensification of dream activity during clozapine therapy. REM sleep was found to be increased to 85% of the total sleep time. In these patients, the onset of REM sleep occurred almost immediately after falling asleep.

INDICATIONS AND USAGE

Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. Because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard antipsychotic drugs, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs. (See **WARNINGS**)

The effectiveness of clozapine in a treatment resistant schizophrenic population was demonstrated in a 6-week study comparing clozapine and chlorpromazine. Patients meeting DSM-III criteria for schizophrenia and having a mean BPRS total score of 61 were demonstrated to be treatment resistant by history and by open, prospective treatment with haloperidol before entering into the double-blind phase of the study. The superiority of clozapine to chlorpromazine was documented in statistical analyses employing both categorical and continuous measures of treatment effect.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated.

CONTRAINDICATIONS

Clozapine is contraindicated in patients with myeloproliferative disorders, uncontrolled epilepsy, or a history of clozapine induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

Clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (*SEE FOLLOWING*), CLOZAPINE SHOULD BE RESERVED FOR USE IN THE TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY BEFORE INITIATING TREATMENT WITH CLOZAPINE, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD ANTIPSYCHOTIC DRUG PRODUCT, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION.

PATIENTS WHO ARE BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) AND DIFFERENTIAL COUNT BEFORE INITIATION OF TREATMENT, AND A WBC COUNT EVERY WEEK THROUGHOUT TREATMENT, AND FOR 4 WEEKS AFTER THE DISCONTINUATION OF CLOZAPINE.

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES WEEKLY WBC TESTING PRIOR TO DELIVERY OF THE NEXT WEEK'S SUPPLY OF MEDICATION.

Agranulocytosis

Agranulocytosis, defined as an absolute neutrophil count (ANC) of less than 500/mm³, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 16 US cases out of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. This reaction could prove fatal if not detected early and therapy interrupted. Of the 148 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of clozapine induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. Nevertheless, it is unknown at present what the case fatality rate will be for clozapine induced agranulocytosis, despite strict adherence to the recommendation for weekly monitoring of WBC counts. In the US, under a weekly WBC monitoring system with clozapine, there have been 317 cases of agranulocytosis as of January 1, 1994; 11 were fatal. During this period, over 60,000 patients received clozapine.

Because of the substantial risk of agranulocytosis in association with clozapine use, which may persist over an extended period of time, patients must have a blood sample drawn for a WBC count before initiation of treatment with clozapine, and must have subsequent WBC counts done at least weekly for the duration of therapy, as well as for 4 weeks thereafter. The distribution of clozapine is contingent upon performance of the required blood tests.

Treatment should not be initiated if the WBC count is less than 3500/mm³, or if the patient has a history of a myeloproliferative disorder, or previous clozapine induced agranulocytosis or granulocytopenia. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection. If, after the initiation of treatment, the total WBC count has dropped below 3500/mm³ or it has dropped by a substantial amount from baseline, even if the count is above 3500/mm³, or if immature forms are present, a repeat WBC count and a differential count should be done. A substantial drop is defined as a single drop of 3,000 or more in the WBC count or a cumulative drop of 2,000 or more within 3 weeks. If subsequent WBC counts and the differential count reveal a total WBC count between 2000 and 3500/mm³ and an ANC above 1500/mm³, twice weekly WBC counts and differential counts should be performed.

If the total WBC count falls below 2000/mm³ or the ANC below 1000/mm³, clozapine therapy should be interrupted. WBC count and differential should be performed daily, and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Clozapine therapy may be resumed if no symptoms of infection develop, and if the total WBC count returns to levels above 3500/mm³ and the ANC returns to levels above 1500/mm³. However, in this event, twice-weekly WBC counts and differential counts should continue until total WBC counts return to levels above 3500/mm³.

If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients whose total WBC counts fall below 2000/mm³, or ANCs below 1000/mm³ during clozapine therapy should have daily WBC count and differential. These patients should not be rechallenged with clozapine. Patients discontinued from clozapine therapy due to significant WBC suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during clozapine therapy, a single, national master file will be maintained confidentially.

Except for evidence of significant bone marrow suppression during initial clozapine therapy, there are no established risk factors, based on world-wide experience, for the development of agranulocytosis in association with clozapine use. However, a disproportionate number of the US cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of clozapine. Most of the US cases occurred within 4-18 weeks of exposure, but neither dose nor duration is a reliable predictor of this problem. No patient characteristics have been clearly linked to the development of agranulocytosis in association with clozapine use, but agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly and in patients who are cachectic or have serious underlying medical illness; such patients may also be at particular risk with clozapine.

To reduce the risk of agranulocytosis developing undetected, clozapine is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication.

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count of 4,000/mm³, clozapine therapy should be interrupted until the eosinophil count falls below 3,000/mm³.

Seizures

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1743 patients exposed to clozapine during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used. Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (see DOSAGE AND ADMINISTRATION).

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking clozapine, with patients having an average increase in pulse rate of 10-15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of clozapine treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of clozapine. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias and sudden death. In addition there have been postmarketing reports of congestive heart failure, myocarditis, with or without eosinophilia, and pericarditis/pericardial effusions in association with clozapine use. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

Clozapine should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that clozapine may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine blocking effect and the clinical finding of a virtual absence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on clozapine who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that clozapine is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown. Given these considerations, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic clozapine use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on clozapine, drug discontinuation should be considered. However, some patients may require treatment with clozapine despite the presence of the syndrome.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Fever

During clozapine therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving clozapine, usually in combination with lithium or other CNS-active drugs. [See **Neuroleptic Malignant Syndrome (NMS)**, under **WARNINGS**.]

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993 there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 10-54 years of age. Based upon the extent of use observed in the Clozaril National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1, 42.2). Deep vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

Hyperglycemia

Severe hyperglycemia, sometimes leading to ketoacidosis, has been reported during clozapine treatment in patients with no prior history of hyperglycemia. While a causal relationship to clozapine use has not been definitively established, glucose levels normalized in most patients after discontinuation of clozapine, and a rechallenge in one patient produced a recurrence of hyperglycemia. The effect of clozapine on glucose metabolism in patients with diabetes mellitus has not been studied. The possibility of impaired glucose tolerance should be considered in patients receiving clozapine who develop symptoms of hyperglycemia, such as polydipsia, polyuria, polyphagia, and weakness. In patients with significant treatment-emergent hyperglycemia, the discontinuation of clozapine should be considered.

Hepatitis

Caution is advised in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and pre-existing liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

Anticholinergic Toxicity

Clozapine has very potent anticholinergic effects and great care should be exercised in using this drug in the presence of prostatic enlargement or narrow angle glaucoma. In addition, clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (see **ADVERSE REACTIONS**). On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Interference with Cognitive and Motor Performance

Because of initial sedation, clozapine may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness

Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using clozapine in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia

Caution is advised in patients being administered general anesthesia because of the CNS effects of clozapine. Check with the anesthesiologist regarding continuation of clozapine therapy in a patient scheduled for surgery.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe clozapine:

- Patients who are to receive clozapine should be warned about the significant risk of developing agranulocytosis. They should be informed that weekly blood tests are required to monitor for the occurrence of agranulocytosis, and that clozapine tablets will be made available only through a special program designed to ensure the required blood monitoring. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
- Patients should be informed of the significant risk of seizure during clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.

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- Patients should be informed that if they stop taking clozapine for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.
- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast feed an infant if they are taking clozapine.

Drug Interactions

The risks of using clozapine in combination with other drugs have not been systematically evaluated.

The mechanism of clozapine induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function.

Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.

Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Because clozapine is highly bound to serum protein, the administration of clozapine to a patient taking another drug which is highly bound to protein (e.g., warfarin, digitoxin) may cause an increase in plasma concentrations of these drugs, potentially resulting in adverse effects. Conversely, adverse effects may result from displacement of protein-bound clozapine by other highly bound drugs.

Cimetidine and erythromycin may both increase plasma levels of clozapine, potentially resulting in adverse effects.

Although concomitant use of clozapine and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in clozapine plasma levels. Phenytoin may decrease clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose.

A subset (3%-10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.

Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, co-administration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

Clozapine may also potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug induced hypotension because of a possible reversal epinephrine effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at doses of approximately 2-4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.

Nursing Mothers

Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving clozapine should not breast feed.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Sixteen percent of 1080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to clozapine treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.

Commonly Observed

Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.

Incidence in Clinical Trials

The following table enumerates adverse events that occurred at a frequency of 1% or greater among clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (N=842)

(Percentage of Patients Reporting)

Body System Adverse Event[a]	Percent
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed sleep/Nightmares	4
Restlessness	4
Hypotonesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry mouth	6
Visual disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[c]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight gain	4
Tongue numb/sore	1

[a] Events reported by at least 1% of clozapine patients are included.

[b] Rate based on population of approximately 1700 exposed during premarket clinical evaluation of clozapine.

Other Events Observed During the Premarketing Evaluation of Clozapine

This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies, a causal relationship to clozapine treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.

Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, hesitancy movements, libido increase or decrease, paranoia, shakiness, Parkinsonism and irritability.

Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nose bleed.

Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hoarseness, gastric ulcer, bitter taste, and eructation.

Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.

Autonomic Nervous System: numbness, polydypsia, hot flashes, dry throat, and myoclonus.

Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.

Musculoskeletal System: twitching and joint pain.

Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.

Hemic and Lymphatic System: anemia and leukocytosis.

Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.

Postmarketing Clinical Experience

Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:

Central Nervous System: delirium; EEG abnormal; exacerbation of psychosis; myoclonws; overdose; paresthesia; possible mild cataplexy; and status epilepticus.

Cardiovascular System: atrial or ventricular fibrillation and peripheral edema.

Gastrointestinal System: acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.

Hepatobiliary System: cholestasis; hepatitis; jaundice.

Hepatic System: cholestasis.

Urogenital System: acute interstitial nephritis and priapism.

Integumentary (Skin): hypersensitivity reactions; photosensitivity; vasculitis, erythema multiforme, and Stevens-Johnson Syndrome.

Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.

Respiratory System: aspiration and pleural effusion.

Hemic and Lymphatic System: deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.

Miscellaneous: CPK elevation; hyperglycemia; hypercalcemia; hyponatremia; and weight loss.

DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence have not been reported or observed in patients taking clozapine.

OVERDOSAGE

Human Experience

The most commonly reported signs and symptoms associated with clozapine overdose are: altered states of consciousness, including drowsiness; delirium and coma; tachycardia; hypotension; respiratory depression or failure; hypersalivation. Aspiration pneumonia and cardiac arrhythmias have also been reported. Seizures have occurred in a minority of reported cases. Fatal overdoses have been reported with clozapine, generally at doses above 2500 mg. There have also been reports of patients recovering from overdoses well in excess of 4 g.

Management of Overdose

Establish and maintain an airway; ensure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdosage. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. Additional surveillance should be continued for several days because the risk of delayed effects. Avoid epinephrine and derivatives when treating hypotension, and quinidine and procainamide when treating cardiac arrhythmia.

There are no specific antidotes for clozapine. Forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

In managing overdosage, the physician should consider the possibility of multiple drug involvement.

Up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physicians' Desk Reference®. *

DOSAGE AND ADMINISTRATION

In order to minimize the risk of agranulocytosis, clozapine is available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication. Upon initiation of clozapine therapy, up to a 1 week supply of additional clozapine tablets may be provided to the patient to be held for emergencies (e.g., weather, holidays).

Initial Treatment

It is recommended that treatment with clozapine begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25-50 mg/day, if well-tolerated, to achieve a target dose of 300-450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice-weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.

In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard antipsychotic drug treatment, patients were titrated during the first 2 weeks up to a maximum dose of 500 mg/day, on a t.i.d. basis, and were then dosed in a total daily dose range 100-900 mg/day, on a t.i.d. basis thereafter, with clinical response and adverse effects as guides to the correct dosing.

Therapeutic Dose Adjustment

Daily dosing should continue on a divided basis as an effective and tolerable dose level is sought. While many patients may respond adequately at doses between 300-600 mg/day, it may be necessary to raise the dose to the 600-900 mg/day range to obtain an acceptable response. [Note: In the multicenter study providing the primary support for the superiority of clozapine in treatment resistant patients, the mean and the median clozapine doses were both approximately 600 mg/day.]

Because of the possibility of increased adverse reactions at higher doses, particularly seizures, patients should ordinarily be given adequate time to respond to a given dose level before escalation to a higher dose is contemplated.

Dosing should not exceed 900 mg/day.

Because of the significant risk of agranulocytosis and seizure, events which both present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided.

Maintenance Treatment

While the maintenance effectiveness of clozapine in schizophrenia is still under study, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on clozapine, but at the lowest level needed to maintain remission. Because of the significant risk associated with the use of clozapine, patients should be periodically reassessed to determine the need for maintenance treatment.

Discontinuation of Treatment

In the event of planned termination of clozapine therapy, gradual reduction in dose is recommended over a 1-2 week period. However, should a patient's medical condition require abrupt discontinuation (e.g., leukopenia), the patient should be carefully observed for the recurrence of psychotic symptoms.

Reinitiation of Treatment in Patients Previously Discontinued

When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (see WARNINGS). If that dose is well tolerated, it may be feasible to titrate patients back to a therapeutic dose more quickly than is recommended for initial treatment. However, any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, should be re-titrated with extreme caution after even 24 hours of discontinuation.

Certain additional precautions seem prudent when reinitiating treatment. The mechanisms underlying clozapine induced adverse reactions are unknown. It is conceivable, however, that re-exposure of a patient might enhance the risk of an untoward event's occurrence and increase its severity. Such phenomena, for example, occur when immune mediated mechanisms are responsible. Consequently, during the reinitiation of treatment, additional caution is advised.

Patients discontinued for WBC counts below 2000/mm^3 or an ANC count below 1000/mm^3 must *not* be restarted on clozapine. (See WARNINGS)

HOW SUPPLIED

Clozapine Tablets are available only through a distribution system that ensures weekly WBC testing prior to delivery of the next week's supply of medication.

Clozapine Tablets are available as pale yellow, round tablets, debossed "4359" on one side and "25" and a bisect on the other, containing 25 mg clozapine packaged in bottles of 100, 500, 1000 and 5000 tablets.

Clozapine Tablets are available as pale yellow, round, flat-faced, beveled-edge tablets with a bisect, debossed "4360" on one side and "100" on the other, containing 100 mg clozapine packaged in bottles of 100, 500, 1000, and 4000 tablets.

PHARMACIST: Dispense in a tight container as defined in the USP. Use child-resistant closure (as required).

Drug dispensing should not ordinarily exceed a weekly supply.

Dispensing should be contingent upon the results of a WBC count.

Store at controlled room temperature 15°-30°C (59°-86°F).

CAUTION: Federal law prohibits dispensing without prescription.

* Trademark of Medical Economics Company, Inc.

MANUFACTURED BY
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

0172
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D3

CLOZAPINE TABLETS

CLOZAPINE TABLETS
0193-03

0193-03
CLOZAPINE
TABLETS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074949

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO.

   Two (2)

2. ANDA #74-949

3. NAME AND ADDRESS OF APPLICANT

   Zenith Goldline Pharmaceuticals, Inc.,
   Attention: Jason Gross
   140 Legrand Avenue,
   Northvale, NJ 07647

4. LEGAL BASIS FOR SUBMISSION

   The listed reference product is Clozaril® Tablets, 25mg and 100mg Manufactured by Novartis (used to be Sandoz) Pharmaceuticals, Corporation. Clozaril® is not covered by any patents or exclusivity provisions.

5. SUPPLEMENT(s)

   None

6. PROPRIETARY NAME

   None

7. NONPROPRIETARY NAME

   Clozapine Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

   None

9. AMENDMENTS AND OTHER DATES:

   Minor Amendment - June 2, 1997
   Telephone amendment (bioequivalence) - July 30, 1997
   Telephone amendment - November 5, 1997
   Telephone amendment - November 21, 1997

10. PHARMACOLOGICAL CATEGORY

    Antipsychotic

11. Rx or OTC

    Rx

12. RELATED IND/NDA/DMF(s)

DMF#(type)	Product	DMF holder	LOA

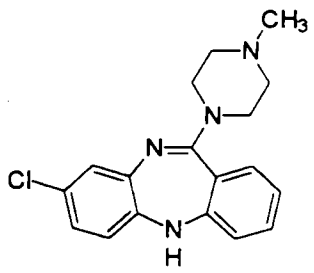
13. DOSAGE FORM

Tablets

14. POTENCY

25mg and 100mg

15. CHEMICAL NAME AND STRUCTURE



$C_{18}H_{19}ClN_4$ 326.83 *[5786-21-0]*
5*H*-Dibenzo[*b*,*e*][1,4]diazepine, 8-chloro-11-(4-methyl-1-piperazinyl)-.
Refer to USAN 1991, page 157.

16. RECORDS AND REPORTS

None

17. COMMENTS

This application was found to be approvable.
Labeling was reviewed and found to be satisfactory (11/3/97, reviewed by L. Golson).
The telephone amendment of November 5, 1997 was reviewed and found to be acceptable. The amendment was related to the specifications of other individual unknown impurities for the drug substance and the drug product at the time of release and on stability. The telephone amendment of November 21, 1997 was reviewed and found to be satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable.

19. REVIEWER: DATE COMPLETED:

Liang-Lii Huang, Ph.D. November 25, 1997

cc:
ANDA 74-949
ANDA (DUP) 74-949
DIV FILE
Field Copy
Endorsements (Draft and Final with Dates):

HFD-627 /Liang-Lii Huang, Ph.D./ 11/25/97 11/25/97
HFD-627 /Paul Schwartz, Ph.D./11/25/97 11/25/97
CHEMISTRY REVIEW - APPROVABLE

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Date: November 25, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074949

BIOEQUIVALENCE REVIEW(S)

HALF TABLETS COMPARATIVE DISSOLUTION STUDIES

METHOD: USP APPARATUS 1, 100 RPM, 1000 mL pH 4.0 Acetate Buffer (0.05M), 37°C
ANALYTICAL METHOD:
TOLERANCE: NLT (Q) in 45 Minutes
PROCEDURE: The tablets were broken in halves and the portion which are within ±3% of half of average tablets weight were selected for dissolution

ZENITH'S PRODUCT:
Clozapine Tablets, 25 mg (½ Tablet)
Batch #: ND-234
Master Formula #: ND-4359-1B
Test Date: July 2, 1997

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	97.1	97.4	97.4	97.4	97.6
RANGE					
RSD	2.1	2.2	2.1	2.1	2.1

REFERENCE PRODUCT:
Clozaril Tablets, 25 mg (½ Tablet)
Batch #: 081U4750; Exp.: 1/97
Master Formula: N/A
Test Date: July 2, 1997

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	101.4	101.3	101.2	101.7	101.7
RANGE					
RSD	1.96	2.1	1.9	1.6	1.6

This is the transcription of the laboratory records.

Transcription checked by:___ DATE: 7/10/97

HALF TABLETS COMPARATIVE DISSOLUTION STUDIES

METHOD: USP APPARATUS 1, 100 RPM, 1000 mL pH 4.0 Acetate Buffer (0.05M), 37°C

ANALYTICAL METHOD:

TOLERANCE: NLT (Q) in 45 Minutes

PROCEDURE: The tablets were broken in halves and the portion which are within ±3% of half of average tablets weight were selected for dissolution

ZENITH'S PRODUCT:
Clozapine Tablets, 100 mg (½ Tablet)
Batch #: ND-388
Master Formula #: ND-4360-3C
Test Date: July 10, 1997

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	55.7	91.2	103.5	103.5	103.5
RANGE					
RSD	4.8	3.8	1.5	1.4	1.5

REFERENCE PRODUCT:
Clozaril Tablets, 100 mg (½ Tablet)
Batch #: 094Z3020; Exp.: 4/2000
Master Formula: N/A
Test Date: July 17,1997

(PERCENT DISSOLVED IN MINUTES)

NO.	10'	20'	30'	45'	60'
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
MEAN	96.4	100.1	100.1	100.2	100.3
RANGE					
RSD	3.6	2.4	2.4	2.3	2.3

This is the transcription of the laboratory records.

Transcription checked by:_____ DATE:_____

SEP 18 1997

Clozapine Tablets	Zenith Goldline
25 mg and 100 mg Tablets	Northvale, NJ
ANDA #74-949	Submission Date:
Reviewer: Moo Park	5/28/97; 6/2/97; 7/30/97
Filename: 74949a.597	

Review of an Amendment

I. Objectives

Review of Zenith's amendment responding to the bio deficiency letter dated 2/20/97 and dissolution data on scored tablets submitted on 6/2/97 and 7/30/97.

II. Background

Zenith's original submission dated 8/22/96 was reviewed by the Division of Bioequivalence and six deficiencies were cited. It was also found that the firm initially manufactured unscored 100 mg tablets and scored 25 mg tablets. The firm was requested to manufacture scored 100 mg tablets to match the reference product by the Division of Labeling. The firm submitted dissolution data for intact scored 100 mg tablets on 6/2/97. The firm was requested to submit additional dissolution data for half tablets of 25 mg and 100 mg scored tablets by the Division of Bioequivalence as of 7/1/97. Dissolution data for the half tablets were submitted by the firm as of 7/30/97.

III. Review of the Data Submitted in the Amendment

Zenith provided its response to each of the six deficiencies as follows:

1. Response to Deficiency 1 (Submit assay method for review.):

The submitted assay method is acceptable.

2. **Response to Deficiency 2**(Explain clearly why it is not possible to generate recovery data.):

The response is satisfactory and acceptable.

3. **Response to Deficiency 3**(Submit stability data of internal standard and stability data of stock solutions of clozapine and the internal standard.):

Submitted stability data are acceptable.

4. **Response to Deficiency 4**(Stability study should be performed using samples of a wide concentration range such as the quality control samples. Some of the stability data were based on only one concentration.):

The applicant submitted the following stability data to supplement the original stability data as shown in Table 1.

Table 1. Stability Data

Submitted stability data are acceptable.

5. **Response to Deficiency 5**(Clarify the meaning of assayed individual curve and assayed combined curve.):

The response is satisfactory and acceptable.

6. **Response to Deficiency 6**(Submit data showing intra- and inter-day variability for pre-study and within-study validation.):

The response is satisfactory and acceptable.

IV. Dissolution data for the scored tablets

The dissolution data for half tablets of 25 mg and 100 mg strengths scored tablets and unbroken 100 mg scored tablets were submitted as summarized in Table IV-1 using the following FDA dissolution specifications:

Medium and Volume	Acetate Buffer, pH 4.0; 1000 mL
Apparatus and rpm	1 (basket); 100 rpm
Tolerances	NLT in 45 min
Assay Method	

Data for the half tablets of 25 mg and 100 mg strengths scored tablets and unbroken 100 mg scored tablets met the FDA specifications.

V. Deficiencies

None.

VI. Recommendations

1. The *in vivo* bioequivalence study conducted under fasting conditions by Zenith Goldline on its Clozapine Tablets, 25 mg strength, lot #ND-234, comparing it to Sandoz's Clozaril®, 25 mg tablets, lot #081U4750, has been found acceptable. The studies demonstrate that Zenith's Clozapine Tablets, 25 mg strength, is bioequivalent to Sandoz's Clozaril®, 25 mg tablets.

2. The dissolution testing conducted by Zenith on its Clozapine Tablets, 25 mg strength, lot #ND-234, and 100 mg strength, lot #ND-322, is acceptable. The formulation for the 100 mg strength tablets is proportionally similar to the 25 mg strength tablets of the test product which underwent the acceptable bioequivalence study (submission date:8/22/96). The waiver of in vivo bioequivalence study requirements for the 100 mg strength tablets of the test product is granted. The 100 mg strength tablets of the test product are therefore

deemed bioequivalent to Sandoz's Clozaril®, 100 mg tablets.

3. The FDA dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of pH 4.0 Acetate Buffer at 37°C using USP 23 Apparatus I (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

The firm should be informed of the recommendations.

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RD INITIALED RMHATRE
FT INITIALED RMHATRE 8/28/97
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Division of Bioequivalence

Concur: _____ Date: 9/18/97
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA #74-949 (original, duplicate), Park, Drug File, Division File, HFD-650 (Director)

File history: Draft (8/18/97); Final (8/27/97)

Table VI-1. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Clozapine Tablets					
Strength	25 mg and 100 mg					
ANDA Number	74-949					
Applicant	Zenith Goldline					
Reference Drug Product	Sandoz's Clozaril					
II. FDA Method for Dissolution Testing						
Medium and Volume	Acetate Buffer, pH 4.0; 1000 mL					
Apparatus and rpm	1 (basket); 100 rpm					
Tolerances	NLT in 45 min					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: ND-234 Strength: 25 mg, scored No of Units: 12 whole tablets			Reference Product Lot No: 081U4750 Strength: 25 mg, scored No of Units: 12 whole tablets		
min	Mean	Range	%CV	Mean	Range	%CV
10	97.5		1.1	101		1.6
20	97.4		1.2	101		1.4
30	97.2		1.1	101		1.3
45	97.2		1.1	101		1.3
Time	Test Product Lot No: ND-322 Strength: 100 mg, unscored No of Units: 12 whole tablets			Reference Product Lot No: 351Y9985 Strength: 100 mg, scored No of Units: 12 whole tablets		
min	Mean	Range	%CV	Mean	Range	%CV
10	54.8		3.9	39.1		8.2

20	93.3		3.9	68.8		7.0
30	102		1.5	92.4		6.9
45	102		1.5	102.8		1.5

Time	Test Product Lot No: ND-234 Strength: 25 mg, scored No of Units: 12 half tablets			Reference Product Lot No: 081U4750 Strength: 25 mg, scored No of Units: 12 half tablets		
min	Mean	Range	%CV	Mean	Range	%CV
10	97.1		2.1	101.4		2.0
20	97.4		2.2	101.3		2.1
30	97.4		2.1	101.2		1.9
45	97.4		2.1	101.7		1.6

Time	Test Product Lot No: ND-388 Strength: 100 mg, unscored No of Units: 12 half tablets			Reference Product Lot No: 094Z3020 Strength: 100 mg, scored No of Units: 12 half tablets		
min	Mean	Range	%CV	Mean	Range	%CV
10	55.7		4.8	96.4		3.6
20	91.2		3.8	100.1		2.4
30	103.5		1.5	100.1		2.4
45	103.5		1.4	100.2		2.3